National PBM Drug Monograph
Duloxetine (Cymbalta) for the Treatment of Major Depressive Disorder
January 2005
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Also see related monograph of duloxetine on neuropathic pain and therapeutic guidelines for depression at www.vapbm.org or vaww.pbm.med.va.gov.

Executive Summary:

Duloxetine is a dual inhibitor of serotonin and norepinephrine reuptake indicated for the treatment of major depressive disorder and pain due to diabetic peripheral neuropathy. Anticipated off-label uses include other forms of neuropathic pain such as fibromyalgia, anxiety disorder, bipolar depression and stress urinary incontinence.

Duloxetine is metabolized by cytochrome P450 2D6 and 1A2 isozymes and is ultimately eliminated in the urine and feces.

Duloxetine is taken orally and should be initiated as 20 mg twice daily (40 mg per day) and can be increased to 30 mg twice a day or 60 mg once per day.

Six clinical trials studied duloxetine in doses of 60 to 120 mg per day for 8 to 9 weeks in duration for the treatment major depressive disorder. By the end of these trials, duloxetine was shown to be superior to placebo in reducing the total $HAMD_{17}$ scores. Duloxetine differed significantly from placebo in response and remission rates in 3 of the 6 trials ($p<0.05$). Duloxetine resulted in response rates of 45% to 65% and remission rates of 31% to 56%. Placebo resulted in response rates of 23% to 48% and remission rates of 15% to 32%. A 52-week, open-label study with a primary objective to evaluate duloxetine's safety and secondary objective of measuring its efficacy resulted in a response rate of 71% and a remission rate of 60%.

Similar to other antidepressant that affect serotonin and/or norepinephrine reuptake, common adverse events reported for duloxetine include nausea, dry mouth, constipation, diarrhea, vomiting, decreased appetite, dizziness, somnolence, insomnia, sweating, and sexual dysfunction. Duloxetine has the potential to increase systolic and diastolic blood pressures, and heart rate.

Duloxetine is contraindicated in patients with a known hypersensitivity to duloxetine capsules, patients who are concurrently taking or have taken a monoamine oxidase inhibitor (MAOI) in the past 14 days, or who have uncontrolled narrow-angle glaucoma.

Duloxetine has demonstrated efficacy superior to placebo in clinical trials. Trials comparing duloxetine to other available antidepressants have either not been designed to compare the two groups or were not adequately powered for such comparisons. Duloxetine has not been studied in patients with refractory depression, multiple co-morbid conditions, or in patients with depression and a diagnosis involving chronic pain such as arthritis or fibromyalgia. Duloxetine's use in the treatment of depressed Veterans is limited by the lack of this information and its greater cost than other available antidepressants.

Duloxetine, as an antidepressant, is not on the VA National Formulary; VISNs do not have the option of adding duloxetine to VISN Formularies.

Introduction[1,2]

Duloxetine is approved for the treatment of depression and neurpathic pain. Both conditions affect large numbers of individuals, with considerable overlap. Duloxetine, like venlafaxine, is thought to work by inhibiting both norepinephrine and serotonin reuptake (a SNRI). Unlike venlafaxine, duloxetine is believed to have this activity across its dosing spectrum, rather than only at higher doses. The reuptake inhibition of norepinephrine appears to be critical for duloxetine's efficacy in the treatment of chronic and neuropathic pain, a property it shares with other antidepressants such as certain tricyclic antidepressants and venlafaxine.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating duloxetine for possible addition to the VA National Formulary; (2) define its role in the treatment of depression; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1-8]

Mechanism of Action

Duloxetine is a dual inhibitor of serotonin and norepinephrine reuptake (Table 1). This reuptake inhibition results in enhanced release of serotonin and norepinephrine in the limbic areas of the rat brain which are thought to be responsible for its antidepressant effects. Duloxetine is a weak inhibitor of dopamine reuptake with no significant affinity for the dopamine, histamine, or muscarinic receptors *in vitro*. Duloxetine is not a monoamine oxidase inhibitor.

Table 1. Duloxetine, venlafaxine and other selected antidepressant inhibitory (K) and affinity constants for serotonin and norepinephrine

Antidepressant	NE transporter (nM)	5-HT transporter (nM)	NE/5-HT Ratio
Duloxetine	7.5	0.8	9.4
Venlafaxine	2480	82	30
Nortriptyline	4.35	18.5	0.235
Desipramine	0.83	17.5	0.05
Fluoxetine	244	0.81	301
Paroxetine	40	0.125	320
Citalopram	4000	1.16	3448
Sertraline	417	0.293	1423

K_i – inhibitory constant; the smaller the constant the greater the affinity/inhibition

Table 2. Duloxetine's Pharmacokinetic Parameters

Parameter	Duloxetine
Bioavailability	90.5%, 50% (30-80)
Tmax	6 hours (median)
Protein Binding	>90%
Metabolism	CYP2D6, 1A2
Elimination	Renal and Fecal
Half-life	12.5 hours (9.2 – 19.1)
Volume of Distribution	1943 L (803 – 3531)
Clearance	114 L/h (44 – 218)

FDA Approved Indication(s) and Off-label Uses[1,2]

Duloxetine is indicated for the treatment of major depressive disorder and pain due to diabetic peripheral neuropathy.

Anticipated off-label uses include other forms of neuropathic pain such as fibromyalgia. Off-label psychiatric uses may include anxiety disorders and bipolar depression. Duloxetine has been investigated for the treatment of urinary stress incontinence.

Current VA National Formulary Alternatives

Table 3. Current other alternative antidepressants on the VA National formulary

Serotonin Reuptake Inhibitors	Tricyclic Antidepressants	Agents Affecting Serotonin and Norepinephrine	Dopamine Re-uptake Inhibitors
Fluoxetine	Amitriptyline	Venlafaxine (SNRI)	Bupropion
Paroxetine	Imipramine	Mirtazapine	
Citalopram	Desipramine	Nefazodone	
Sertraline	Nortriptyline		
	Clomipramine		

Dosage and Administration[1]

Major Depressive Disorder: Duloxetine is taken orally and should be initiated as 20 mg twice daily (40 mg per day) and can be increased to 30 mg twice a day or 60 mg once per day. There is no evidence of additional antidepressant properties in doses greater than 60 mg per day. Duloxetine can be taken with or without food (See also Drug Interactions). Treatment duration should be individualized, but should be continued for 4 to 9 months after the patient's initial response.

Dose in Renal Impairment: Duloxetine is not recommended for patients with end stage renal disease. Dose adjustments are not necessary for patients with lesser degrees of renal impairment.

Dose in Hepatic Impairment: Duloxetine is not recommended for patients with any hepatic insufficiency.

Dose for the Elderly: A dose adjustment is not necessary.

Efficacy

Efficacy Measures

Major Depressive Disorder:

- Hamilton Depression Rating Scale ($HAMD_{17}$) – an observer rated 17-item scale that assesses mood, sleep, anxiety, suicidality, cognitive and physical retardation, and somatic symptoms.
    - Response defined as a 50% or greater reduction in $HAMD_{17}$ score
    - Remission defined as a $HAMD_{17}$ score $\leq$6 or 7.
- Montgomery Asberg Depression Rating Scale (MADRS) – a 10-item scale, 9 of the items are reported by the patient, that assesses tension, sadness, and other symptoms of depression.
- Clinical Global Impression-severity (CGI-s) – a single item, clinician-related question used to assess response to treatment.

- Patient Global Impression (PGI) - a single item, patient-related question used to assess response to treatment.
- Quality of Life in Depression Scale (QLDS)
- 100 mm Visual Analog Scale (VAS) for pain

Summary of efficacy findings[2,9-14]

Clinical trials comparing duloxetine to placebo, paroxetine or fluoxetine have used similar study designs and inclusion/exclusion criteria which are summarized below:

- Double-blind, placebo-controlled, randomized, parallel-group, fixed-dose, multi-center clinical trials of 8 or 9 weeks duration.
- Inclusion criteria: Men and women ages 18 years or older who met either DSM-IIIR or DSM-IV criteria for major depressive disorder, non-psychotic (confirmed by the Mini International Neuropsychiatric Interview), a $HAMD_{17}$ $\geq$15 and CGI-s $\geq$4
- Exclusion criteria: Another primary Axis I diagnosis other than depression or an anxiety disorder in the previous year, history of substance abuse or dependence within the past year, a failure to respond to 2 or more antidepressants during the current depressive episode, starting or stopping psychotherapy within 6 months prior to enrollment or during the study.
- Concurrent medications: Use of chloral hydrate, temazepam, or zolpidem for insomnia for not more than 6 nights during the study; the use of prescription pain medications was not permitted; patients were allowed to continue antihypertensive medication if they had been taking them at a stable dose for more than 3 months

Outcomes of Depression Trials

(Response and remission rates calculated using last observation carried forward [LOCF])

- Six clinical trials studied duloxetine in doses of 60 to 120 mg per day for 8 to 9 weeks in duration for the treatment major depressive disorder. By the end of these trials, duloxetine was shown to be superior to placebo in reducing the total $HAMD_{17}$ scores. Duloxetine differed significantly from placebo in response and remission rates in 3 of the 6 trials ($p<0.05$). Duloxetine resulted in response rates of 45% to 65% and remission rates of 31% to 56%. Placebo resulted in response rates of 23% to 48% and remission rates of 15% - 32%.
- Another trial consisting of an initial 12-week, open-label phase during which patients with major depression received duloxetine 60 mg once daily. Those meeting predetermined response criteria were then randomized to continue duloxetine 60 mg or placebo for another 26-weeks. In cases of relapse, patients received rescue medication consisting of duloxetine 60 mg twice a day for those already taking duloxetine and duloxetine 60 mg daily for those taking placebo. Rescue medication was continued for 12-weeks or until the 26 week continuation phase was completed. During the acute treatment phase, patients had a response rate of 68% and a remission rate of 53%. During the continuation phase, patients taking duloxetine had a lower relapse rate (17.4%) compared to placebo (28.5%). For those entering the rescue phase, response and remission rates for duloxetine 60 mg twice a day were 62% and 38%, respectively, compared to 77% and 57%, respectively for duloxetine 60 mg daily (previously taking placebo).
- In a 52-week, open-label study with a primary objective to evaluate duloxetine's safety and secondary objective of measuring its efficacy, doses of 40 mg or 60 mg twice a day resulted in a response rate of 71% and a remission rate of 60%.

- One trial has been published comparing duloxetine to paroxetine and placebo. Participants were randomized to duloxetine 20 mg or 40 mg twice a day, paroxetine 20 mg daily, or placebo. After 8-weeks, duloxetine 80 mg per day had a response rate (51%) significantly greater than placebo (31%), p=0.009. The response rates for duloxetine 40 mg daily (44%) and paroxetine (40%) did not differ significantly from placebo (p=0.083 and p=0.204, respectively). The remission rate for duloxetine 80 mg (50%) differed from placebo (30%, p=0.008) and duloxetine 40 mg (35%, p=0.045), but not from paroxetine (37%, p=0.091).
- Another placebo controlled trial included a fluoxetine 20 mg per day treatment arm as an internal control. The fluoxetine arm was not sufficiently powered to allow comparisons to either the placebo or duloxetine arms.

Pain Efficacy in Depression Trials[15, 16]

Change in pain scores, as measured by 100 mm VAS, was measured as a secondary outcome variable in three duloxetine clinical trials in major depressive disorder: one placebo- and active comparator-controlled trial and two placebo-controlled trials. In the three trials, overall pain severity scores for patients taking duloxetine 60 mg and 80 mg were shown to differ significantly from placebo at various time points over the 8 or 9 week study period. Study participants were not required to have a condition or diagnosis associated with pain, or was pain of any severity a criteria for enrollment. As such, the baseline median VAS scores for overall pain ranged from 15 to 22 mm. The median changes from baseline to last observation ranged from -7.5 to -7.0 for duloxetine 60 mg and 80 mg and were significantly different from placebo, -2 to 0. Neither, duloxetine 40 mg or paroxetine 20 mg daily differed from placebo at any time point.

Duloxetine 80 mg was also shown to significantly reduce median shoulder pain scores (-1) and reduce the time in pain while awake (-8) compared to placebo (0 and 0, respectively). In one of the two studies, duloxetine 60 mg significantly reduced median back (-5) pain compared to placebo (0).

A separate analysis pooled data from two identically designed depression trials comparing duloxetine 60 mg once daily to placebo with the objective of assessing the relationship between alleviation of painful physical symptoms and remission rate independent of changes in the core emotional symptoms of depression. After adjusting for changes in core emotional symptoms of depression measured with the HAMD, a synergistic relationship between remission rate and pain relief was identified – a greater improvement in pain scores was still associated with a higher estimated probability of (depression) remission ($p<0.001$). Using LOCF analysis to quantitate these findings, suggests that a patient's chance of remission increased 8% if their endpoint VAS pain score was 10 rather than 25.

Adverse Events (Safety Data)[1,2,17,18]

Deaths and Other Serious Adverse Events

Suicidal or self-injurious ideation was reported by 0.2% and 0.1% of patients treated with duloxetine, respectively, compared to 0.3% an 0% for placebo. There were no suicides or drug-related deaths reported.

Common Adverse Events

Table 4. Adverse Events Reported in Placebo-Controlled Clinical Trials Reported by at least 2% of Participants

Adverse Event	Percentage Reporting	
	Duloxetine (n=1139)	Placebo (n=777)
Nausea	20	7
Dry mouth	15	6
Constipation	11	4
Diarrhea	8	6
Vomiting	5	3
Decreased appetite	8	2
Weight loss	2	1
Fatigue	8	4
Dizziness	9	5
Somnolence	7	3
Tremor	3	1
Sweating	6	2
Hot flushes	2	1
Blurred vision	4	1
Insomnia	11	6
Anxiety	3	2

Sexual Adverse Events

Table 5. Incidence of Adverse Sexual Dysfunction Events Reported by at least 2% of Patients in Placebo-Controlled Trials

Adverse Event	Percentage Reporting			
	Male Patients		Female Patients	
	Duloxetine, n=378	Placebo, n=247	Duloxetine, n=761	Placebo, n=530
Abnormal orgasm	4	1	2	0
Erectile dysfunction	3	1	NA	NA
Decreased libido	6	2	1	0
Ejaculatory dysfunction	4	1	NA	NA
Delayed ejaculation	3	1	NA	NA

Cardiovascular Adverse Events

In the six major depression, placebo-controlled clinical trials, the mean changes in supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) were ~1.5 mm Hg for patients treated with duloxetine. Treatment emergent elevations in SBP for duloxetine was 6.9% versus 3.3% for placebo ($p=.003$) and 4.4% versus 2.3% ($p<.027$) for DBP, respectively. The incidence of sustained hypertension on three consecutive visits did not differ between duloxetine and placebo. Patients treated with duloxetine had a mean increase in heart rate of ~1.5 beats per minute (supine) compared to a mean decrease of 0.5 beats per minute for those taking placebo. Duloxetine was not found to prolong QTc intervals in patients treated for major depressive disorder. The incidence of a change in QTc intervals $\geq$ 30 msec was 4.2% for duloxetine and 5.3% for placebo.

Weight Change

In trials of 8-12 weeks duration, duloxetine treated patients experienced a mean weight loss of 0.54 kg compared to a mean gain of 0.25 kg in patients taking placebo ($p<.001$). At the end of a 52-week open-label trial (duloxetine 80 mg or 120 mg/day) participants gained an average of 2.4 kg.

Tolerability
An analysis combining the six double-blind, placebo or active comparator-controlled trials reported that the incidence of discontinuation due to adverse events of 14.6% for duloxetine compared to 5% for placebo ($p<.001$). Nausea and dizziness were the only two individual adverse events to differ significantly between duloxetine and placebo as a cause for discontinuation.

Precautions/Contraindications[1]

Precautions
In clinical trials duloxetine was reported to elevate liver transaminases resulting in its discontinuation in 0.3% (27/8454) of patients; with a median time of detection of approximately 2 months. Elevations of alanine transaminase (ALT) of greater than 3-times normal occurred in 0.9% (8/930) of duloxetine patients and 0.3% (2/652) placebo-treated patients. The composite of all placebo-controlled trials for any indication found that 1% (39/3732) of patients treated with duloxetine had an ALT greater than 3-times the upper-limit of normal compared to 0.2% (6/2568) of patients treated with placebo. There is evidence from fixed-dose studies that elevations of ALT (>3-fold) and AST (>5-fold) are dose-related.

Duloxetine has been associated with mean increases of 2 mm Hg systolic and 0.5 mm Hg diastolic blood pressure compared to placebo. It is recommended that blood pressure be measured prior to starting duloxetine and periodically throughout treatment.

Duloxetine should be prescribed with caution to patients with a history of a seizure disorder. Persons with seizure disorders were not included in the clinical trials with duloxetine in which 1 out of 1139 (0.1%) patients treated with duloxetine experienced a seizure compared to none in patients treated with placebo.

Activation of mania or hypomania can occur in patients taking antidepressants. Patients with a history of bipolar disorder were excluded from duloxetine clinical trials. New onset mania or hypomania was reported in 0.1% of patients with major depressive disorder treated with duloxetine or placebo.

Duloxetine was associated with mydriasis and should be used with caution in patients with controlled narrow-angle glaucoma.

As with the other antidepressants, abruptly stopping duloxetine is discouraged as it may result in a discontinuation syndrome. Symptoms of this syndrome reported significantly more often than with placebo and by at least 2% of patients taking duloxetine for up to 9-weeks consisted of dizziness, nausea, headache, paresthesia, vomiting, irritability, and nightmares. Patients taking duloxetine should have their dose tapered, rather than abruptly discontinuing the medication.

The manufacturer states that there is limited clinical experience with duloxetine in patients with multiple co-morbid conditions. Furthermore, they caution that there is no information on the effect of alterations in gastric motility on the stability of duloxetine's enteric coating. Duloxetine is hydrolyzed in an acidic media to naphthol and caution is advised about its use in patients with impaired gastric emptying.

Use in Pregnancy and Lactation
Pregnancy Category C. Duloxetine and/or its metabolites are excreted into the breast milk of rats. No information is available on whether duloxetine is excreted into human breast milk. Nursing while on duloxetine is not recommended.

Contraindications
Duloxetine is contraindicated in patients with a known hypersensitivity to duloxetine capsules, patients who are concurrently taking or have taken a monoamine oxidase inhibitor (MAOI) in the past 14 days, or who have uncontrolled narrow-angle glaucoma.

Look-alike / Sound-alike (LA / SA) Error Risk Potential
The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:
LA/SA for generic name duloxetine: fluoxetine, atomoxetine HCl, paroxetine, Dulcolax stool softner
LA/SA for trade name Cymbalta: Symbyax

Drug Interactions[1,5,19]

Drug-Drug Interactions
Duloxetine is metabolized by CYP1A2 and CYP2D6 isozymes, as such interactions with other medications or substances that inhibit, induce or compete for these isozymes can affect duloxetine concentrations. Conversely, duloxetine is a moderate inhibitor of CYP2D6 could potentially affect the elimination of other medications metabolized by this isozyme.

CYP1A2 Inhibitors • Fluvoxamine – increased duloxetine's AUC 6-fold and Cmax by ~2.5-fold. • Quinolones (not all) – may increase duloxetine's AUC and Cmax.
CYP2D6 Inhibitors • Paroxetine – increased duloxetine's concentration by 60%. Similar results would be expected with other CYP2D6 inhibitors.
Drugs Metabolized by CYP2D6 • Desipramine – Duloxetine 60 mg twice a day was shown to increase desipramine's AUC 3-fold, suggesting that duloxetine may inhibit the metabolism of other medications metabolized by CYP2D6. • Tolterodine – Duloxetine 40 mg twice a day increased tolterodine's Cmax, AUC, and half-life, and decreased its clearance. Although these changes were statistically significant, it is unlikely they are clinically significant.
Drugs Metabolized by CYP1A2 • *In vitro* drug interaction studies have shown that duloxetine does not induce and is unlikely to inhibit CYP1A2 activity.
Drugs Metabolized by CYP3A4 • *In vitro* drug interaction studies have shown that duloxetine does not induce and is unlikely to inhibit CYP3A4 activity.

Duloxetine's pharmacokinetics was not affected by lorazepam or temazepam, nor were their pharmacokinetics' affected by duloxetine.

Information on duloxetine's affect on the pharmacokinetics of other drugs that are highly protein bound is not available. It is possible that duloxetine may displace other highly protein bound medications, increasing their unbound concentrations and the risk for adverse events.

Alcohol: When taken several hours apart, duloxetine did not increase the impairment of mental and motor skills caused by alcohol. Three patients receiving duloxetine in clinical trials, for whom there was evidence of heavy alcohol use, developed elevations in transaminase, alkaline phosphatase, and bilirubin; as did two patients taking placebo. Patients should be warned about substantial use of alcohol while taking duloxetine.

Duloxetine should be used with caution by patients taking other CNS-acting medications, including those with a similar mechanism of action.

Dissolution of duloxetine's enteric coating is pH dependent and is triggered when the environmental pH is exceeds 5.5. Coaministration of duloxetine with aluminum- and magnesium-containing antacids or with famotidine had no effect on the rate or extent of duloxetine absorption. The coadministration of duloxetine with proton pump inhibitors has not been studied.

Acquisition Costs

Strength	Dose	Cost/Day/patient ($)	Cost/Year/patient ($)
Duloxetine HCl 20 mg capsule	20 mg twice a day	3.80	1387.00
Duloxetine HCl 30 mg capsule	30 mg twice a day	4.18	1525.70
Duloxetine HCl 60 mg capsule	60 mg once a day	2.09	762.85

Pharmacoeconomic Analysis[17]

There are no prospective cost-efficacy studies of duloxetine in the treatment of major depressive disorders available. In the product dossier provided by the manufacturer, there is reference to a cost effectiveness analysis component in a trial comparing duloxetine 80 mg and 40 mg per day to paroxetine 20 mg per day, and placebo. The conclusion of that analysis was that duloxetine 80 mg per day "consistently tended to be both less costly and more effective" than paroxetine. Duloxetine 40 mg per day "tended to be equally or more effective than paroxetine, but results of greater effectiveness and less costly were only slightly above expected nondifferentiating values." The manufacturer has developed a budget impact model for major depressive disorder.

Conclusions

Duloxetine is the second non-tricyclic SNRI antidepressant to be approved. Duloxetine has demonstrated efficacy superior to placebo in clinical trials. Trials comparing duloxetine to other available antidepressants have either not been designed to compare the two groups or were not adequately powered for such comparisons. Duloxetine has not been studied in patients with refractory depression, multiple co-morbid conditions, or in patients with depression and a diagnosis involving chronic pain such as arthritis or fibromyalgia. Duloxetine's use in the treatment of depressed Veterans is limited by the lack of this information and its greater cost than other available antidepressants.

Formulary Decision on Duloxetine as an Antidepressant

- Duloxetine is not on VA National Formulary.
- VISNs do not have the option of adding duloxetine to VISN Formularies.

References:

1. Duloxetine (Cymbalta) Package Insert. Eli Lilly & Co. 2004.
2. Dugan SE, Fuller MA. Duloxetine: A Dual Reuptake Inhibitor. Ann Pharmacotherapy 2004;38:2078-85.
3. Beique J-C, Lavoie N, de Montigny C, et al. Affinities of venlafaxine and various reuptake inhibitors for the serotonin and norepinephrine transporters. European J Pharmacology 1998;349:129-32.
4. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology 2001;25:871-80.
5. Skinner MH, Kuan H-Y, Pan A, et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clin Pharmacol Ther 2003;73:170-7.
6. Sharma A, Goldberg MJ, Cerimele BJ. Pharmacokinetics and safety of duloxetine, a dual-serotonin and norepinephrine reuptake inhibitor. J Clin Pharmacology 2000;40:161-7.
7. Lantz RJ, Gillespie TA, Rash TJ, et al. Metabolism, excretion, and pharmacokinetics of duloxetine in healthy human subjects. Drug Metabolism and Disposition 2003;31:1142-50.
8. Skinner MH, Kuan HY, Skerjanec A, et al. Effect of age on the pharmacokinetics of duloxetine in women. Br J Clin Pharmacol 2003;57:54-61.
9. Berk M, du Plessis AD, Birkett M, et al. An open-label study of duloxetine hydrochloride, a mixed serotonin and noradrenaline reuptake inhibitor, in patients with DSM-III-R major depressive disorder. Int Clin Psychopharmacology 1997;12:137-40.
10. Detke MJ, Yili L, Goldstein DJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry 2002;63:308-15.
11. Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry 2002;63;225-31.
12. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol 2004;24:389-99.
13. Raskin J, Goldstein DJ, Mallinckrodt CH, et al. Duloxetine in the long-term treatment of major depressive disorder. J Clin Psychiatry 2003;64:1237-44.

14. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatric Res 2002;36:383-90.
15. Fava M, Mallinckrodt CH, Detke MJ, et al. Effect of duloxetine on painful physical symptoms in depressed patients: Do improvements in these symptoms result in higher remission rates. J Clin Psychiatry 2004;65:521-30.
16. Goldstein DJ, Lu Y, Detke MJ, et al. Effects of duloxetine on painful physical symptoms associated with depression. Psychosomatics 2004;45:17-28.
17. Manage Care Dossier: Cymbalta (duloxetine HCl) Delayed-release capsules, pp. 104. September 30, 2004.
18. Nemeroff CB, Schatzberg AF, Goldstein DJ, et al. Duloxetine for the treatment of major depressive disorder. Psychopharmacology Bulletin 2002;36:106-32.
19. Hua TC, Pan A, Chan C, et al. Effect of duloxetine on tolterodine pharmacokinetics in healthy volunteers. Br J Clin Pharmacol 2004;57:652-6.

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